

Synthesis and Insecticidal Activity of Some New 3-[4(3*H*)-Quinazolinone-2-yl]thiomethyl]-1,2,4-triazole-5-thiols

Mustafa M. Ghorab,^a Sami G. Abdel-Hamide,^b Gehad M. Ali^c & El-Sayed H. Shaurub^d

^a Department of Drug Radiation Research, National Center for Radiation Research & Technology, Atomic Energy Authority, Cairo, Egypt

^b Pharmaceutical Chemistry Department, Faculty of Pharmacy, Al-Azhar University, Egypt

^c Division of Radiation Entomology, National Center for Radiation Research & Technology, Atomic Energy Authority, Cairo, Egypt

^d Department of Entomology, Faculty of Science, Cairo University, Egypt

(Received 21 February 1995; revised version received 26 October 1995; accepted 13 March 1996)

Abstract: A series of 14 new 3-[4(3*H*)-quinazolinone-2-yl]thiomethyl]-1,2,4-triazoles were prepared and characterized by elemental analyses, IR, [¹H] NMR and mass spectral data. Four of the compounds showed insecticidal activity equivalent to that of malathion against the adult stage of the blow fly (*Chrysomya albiceps*). However, their activity against the larval stages of this insect species was considerably weaker.

Key words: triazoloquinazolinones, insecticidal activity

1 INTRODUCTION

The quinazoline ring system has important and versatile biological activities.^{1–5} On the other hand, some triazole derivatives are well known as insecticidal agents.^{6–9} In view of these findings, we undertook the synthesis of a new series of compounds incorporating both the quinazolinone and 1,2,4-triazole moieties and evaluated their insecticidal activities against one of the flies which cause myiasis for man and animals, namely, *Chrysomya albiceps* (Wied.). (Diptera: Calliphoridae).

2 EXPERIMENTAL

2.1 Chemical synthesis

All melting points were taken in open capillaries and are uncorrected. Microanalyses were carried out on a Heraeus instrument, and all of the compounds synthesized were found to show correct elemental analyses. IR spectra were recorded on a Pye Unicam SP 1000 using

KBr (ν_{\max} in cm^{-1}). [¹H] NMR spectra were measured in deuterodimethyl sulfoxide solution on a Varian Gemini 200 (200 MHz, [¹H] NMR) using tetramethylsilane as internal standard; chemical shift (δ) in ppm. Mass spectra were run using HP Model: MS-5988. The sequence of reactions leading to the formation of the title compounds is depicted in Fig. 1. All the synthesized compounds are novel. The starting compounds, 3-substituted-6,8-dichloro or 6-iodo-4(3*H*)-quinazolinone-2-thiols (**Ia–d**), were prepared according to reported methods.^{10,11}

2.1.1 Ester derivatives (**IIa–d**)

A mixture of **Ia–d** (0.01 mol), ethyl chloroacetate (0.01 mol) and anhydrous potassium carbonate (2 g) in dry acetone (50 ml) was refluxed for 24 h. The reaction mixture was filtered while hot and the product obtained after concentration of the filtrate was recrystallized from ethanol to give **IIa–d**; (Table 1). The structure of **II** was confirmed on the basis of analytical data and its IR spectrum which revealed the presence of two C=O bands, at 1750 and 1700 cm^{-1} . [¹H] NMR of **IIc**

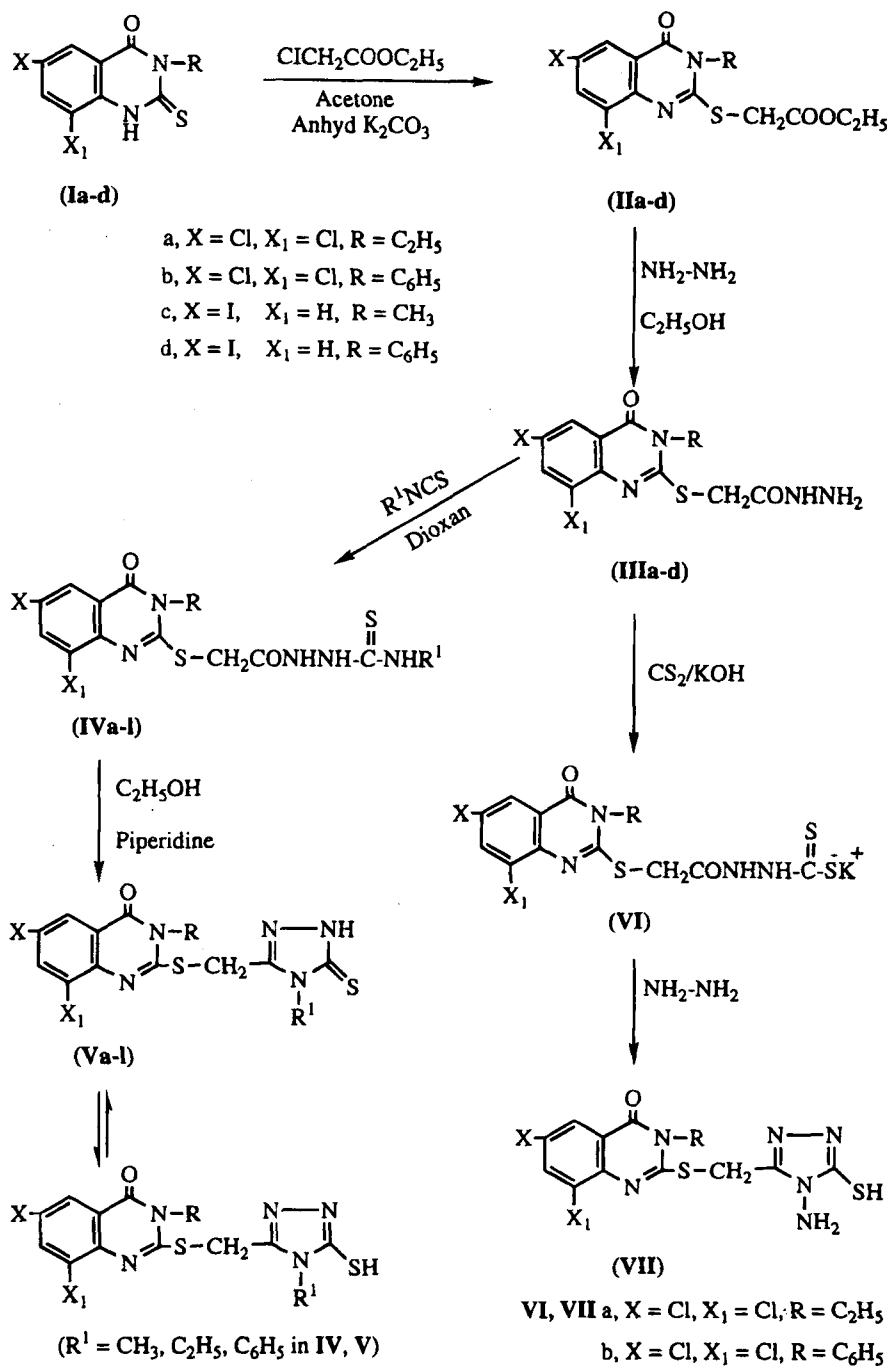


Fig. 1. Overall synthetic routes to 3-[4(3H)-quinazolinone-2-yl]thiomethyl]-1,2,4-triazole-5-thioles.

showed signals at 1.2 [3H, t, CH₃ ester]; 3.5 [3H, s, N-CH₃]; 4.1 [2H, q, CH₂ ester], 4.2 [2H, s, S-CH₂] and 7.2–8.3 [3H, m, Ar-H].

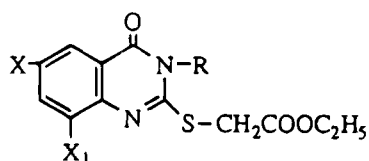
2.1.2 Hydrazone derivatives (IIIa-d)

Hydrazine hydrate (0.012 mol) was added to a solution of IIa-d (0.01 mol) in ethanol (50 ml) and the reaction mixture refluxed for 3 h. The solid obtained was recrystallized from ethanol to give IIIa-d (Table 2). The IR spectra of III revealed the presence of NH and NH₂ bands at 3350 and 3250 cm⁻¹.

2.1.3 Thiosemicarbazide derivatives (IVa-I)

A mixture of IIIa-d (0.01 mol) and the appropriate isothiocyanate (0.01 mol) was refluxed in dry dioxan (50 ml) for 4 h. The solid obtained was recrystallized from acetic acid to give IVa-I (Table 3). The structure assignment of IVa-I was based on analytical data and IR spectra which exhibited bands at 3380, 3320 cm⁻¹ (NH) and 1710, 1680 cm⁻¹ (2C=O). [¹H] NMR of IVa exhibited signals at 1.3 [3H, t, CH₃ ethyl]; 2.9 [3H, s, N-CH₃]; 4.1 [2H, q, CH₂ ethyl]; 4.2 [2H, s, S-CH₂]; 7.9 [2H, m, Ar-H]; 8.1, 9.3 and 10.1 ppm [3H, s, 3NH, D₂O exchangeable]. [¹H] NMR of IVj exhibited

TABLE 1
Physicochemical and Analytical Data for Ester Derivatives



II

Comp.	X	X ₁	R	Yield (%)	m.p. (°C)
IIa	Cl	Cl	C ₂ H ₅	78	151–2
b	Cl	Cl	C ₆ H ₅	72	179–180
c	I	H	CH ₃	81	125–126
d	I	H	C ₆ H ₅	79	129–130

signals at 0.95 [3H, t, CH₃ ethyl], 3.9 [2H, q, CH₂ ethyl]; 4.0 [2H, s, S-CH₂]; 7.4–8.2 [8H, m, Ar-H]; 8.4, 9.3 and 10.1 ppm [3H, s, 3NH, D₂O exchangeable].

2.1.4 1,2,4-Triazole derivatives (Va–l)

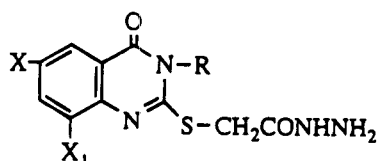
A mixture of IVa–l (0.01 mol) and piperidine (2 ml) in ethanol (10 ml) was refluxed for 6 h, cooled and acidified with dilute hydrochloric acid and the solid obtained was recrystallized from ethanol to give Va–l (Table 4). [¹H] NMR of Va showed signals at 1.3 [3H, t, CH₃ ethyl], 3.5 [3H, s, N-CH₃]; 4.1 [2H, q, CH₂ ethyl]; 4.2 [2H, s, S-CH₂] and 7.9–8.1 ppm [2H, m, Ar-H]. Mass spectra of some triazole derivatives (Va, c, d, h, j) showed molecular ion peaks at *m/z* 402 (36.87%); 464 (14.70%); 450 (9.35%); 459 (5.37%) and 507 (7.89%), respectively.

2.1.5 Potassium [3-ethyl (or phenyl)-6,8-dichloro-4(3H)-quinazolinone-2-yl]thioacetyl dithiocarbazates (VIa, b)

Carbon disulphide (12 ml) was added dropwise to an ice-cold solution of potassium hydroxide (0.015 mol) in

TABLE 2

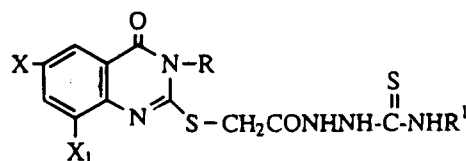
Physicochemical and Analytical Data for Hydrazone Derivatives



III

Comp.	X	X ₁	R	Yield (%)	m.p. (°C)
IIIa	Cl	Cl	C ₂ H ₅	81	186–187
b	Cl	Cl	C ₆ H ₅	83	205–206
c	I	H	CH ₃	86	206–207
d	I	H	C ₆ H ₅	79	209–210

TABLE 3
Physicochemical and Analytical Data for Thiosemicarbazide Derivatives



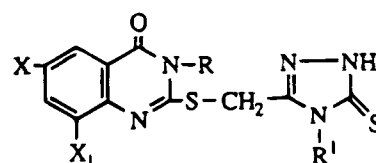
IV

Comp.	X	X ₁	R	R ¹	Yield (%)	m.p. (°C)
IVa	Cl	Cl	C ₂ H ₅	CH ₃	68	203–204
b	Cl	Cl	C ₂ H ₅	C ₂ H ₅	66	193–194
c	Cl	Cl	C ₂ H ₅	C ₆ H ₅	71	266–267
d	Cl	Cl	C ₆ H ₅	CH ₃	73	181–182
e	Cl	Cl	C ₆ H ₅	C ₂ H ₅	80	233–235
f	Cl	Cl	C ₆ H ₅	C ₆ H ₅	76	253–255
g	I	H	CH ₃	CH ₃	68	228–229
h	I	H	CH ₃	C ₂ H ₅	66	221–222
i	I	H	CH ₃	C ₆ H ₅	69	197–199
j	I	H	C ₆ H ₅	CH ₃	71	160–162
k	I	H	C ₆ H ₅	C ₂ H ₅	72	196–197
l	I	H	C ₆ H ₅	C ₆ H ₅	73	187–189

absolute ethanol (100 ml) containing IIIa or b (0.01 mol). The mixture was diluted with absolute ethanol (100 ml) and stirred at room temperature for 14 h to give VIa, b (Table 5).

TABLE 4

Physicochemical and Analytical Data for 1,2,4-Triazole Derivatives

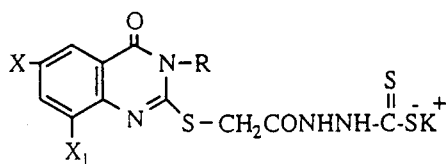


V

Comp.	X	X ₁	R	R ¹	Yield (%)	m.p. (°C)
Va	Cl	Cl	C ₂ H ₅	CH ₃	75	236–237
b	Cl	Cl	C ₂ H ₅	C ₂ H ₅	76	224–225
c	Cl	Cl	C ₂ H ₅	C ₆ H ₅	69	248–250
d	Cl	Cl	C ₆ H ₅	CH ₃	71	306–307
e	Cl	Cl	C ₆ H ₅	C ₂ H ₅	74	267–268
f	Cl	Cl	C ₆ H ₅	C ₆ H ₅	76	236–238
g	I	H	CH ₃	CH ₃	71	232–234
h	I	H	CH ₃	C ₂ H ₅	68	242–243
i	I	H	CH ₃	C ₆ H ₅	73	215–217
j	I	H	C ₆ H ₅	CH ₃	76	239–240
k	I	H	C ₆ H ₅	C ₂ H ₅	71	249–250
l	I	H	C ₆ H ₅	C ₆ H ₅	69	175–177

TABLE 5

Physicochemical and Analytical Data for Potassium[3-ethyl (or phenyl)-6,8-dichloro-4(3H) quinazolinone-2-yl]-thioacetyl Dithiocarbazates

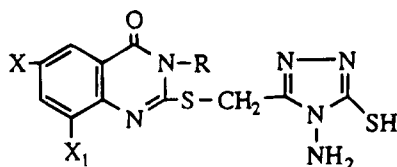


VI

Comp.	X	X ₁	R	Yield (%)	m.p. (°C)
Vla	Cl	Cl	C ₂ H ₅	62	> 310
b	Cl	Cl	C ₆ H ₅	64	> 310

TABLE 6

Physicochemical and Analytical Data for 4-Amino-1,2,4-triazole-5-thiol Derivatives



VII

Comp.	X	X ₁	R	Yield (%)	m.p. (°C)
VIIa	Cl	Cl	C ₂ H ₅	68	170–172
b	Cl	Cl	C ₆ H ₅	59	197–199

2.1.6 4-Amino-1,2,4-triazole-5-thiol derivatives (VIIa, b)

A mixture of VIa, b; (0.01 mol); hydrazine hydrate (0.02 mol) and water (2 ml) was heated under reflux while stirring for 30 min. Cold water (10 ml) was then added and the mixture was neutralized with concentrated hydrochloric acid and the solid obtained was recrystallized from ethanol to give VIIa, b (Table 6). The structure of VII was confirmed on the basis of analytical data and IR spectrum which showed an NH₂ band as double peaks at 3350 and 3250 cm⁻¹. Mass spectrum of VIIa showed a molecular ion peak at *m/z* 403 (0.20%) and a base peak at 273 (100%); other significant peaks appeared at 387 (0.16%); 274 (97.69); 229 (30.88%); 187 (75.17%); 158 (22.23%); 97 (36.45%) and 88 (44.13%).

2.2 Insecticidal activity

The blow fly, *Chrysomya albiceps* (Wied.) was originally obtained from a well-established colony, maintained at 26(±2)°C and 65(±5)% RH in the Entomology Department, Faculty of Science, Cairo University, since 1986, according to Omar.¹²

The insecticidal activity for compounds (Va, Vc, Vj and Vk) was measured on seven-day-old adults and one-day-old third-instar larvae, using a topical application method and dimethylsulfoxide as a solvent.

An organophosphate (malathion) and a carbamate (propoxur) were used as standards. The data were analysed using probit analysis.¹³

3 RESULTS AND DISCUSSION

3.1 Insecticidal activity

The results of the present study (Table 7) show that compounds Va, Vc, Vj and Vk possess adulticidal activ-

TABLE 7
Comparison of Insecticidal Activity of the Synthesized Compounds with Certain Standards against *Chrysomya albiceps* Adults

Comp.	Sex	LD ₅₀ (μg per fly)	95% fiducial limit (μg per fly)	Slope	χ ² (d.f.)
Malathion	Male	2.40	1.70–3.24	1.98	χ ² ₍₄₎ = 1.870
	Female	5.46	4.03–7.39	1.99	χ ² ₍₄₎ = 6.039
Propoxur	Male	0.006	0.004–0.007	1.26	χ ² ₍₆₎ = 2.547
	Female	0.013	0.007–0.025	1.74	χ ² ₍₄₎ = 1.431
Va	Male	2.70	2.01–3.63	3.28	χ ² ₍₄₎ = 5.930
	Female	5.20	4.02–6.73	2.84	χ ² ₍₄₎ = 3.320
Vc	Male	4.20	3.21–5.49	3.28	χ ² ₍₆₎ = 1.667
	Female	4.60	3.16–6.69	3.87	χ ² ₍₆₎ = 2.316
Vj	Male	3.20	2.12–4.82	2.17	χ ² ₍₄₎ = 1.038
	Female	4.50	2.92–6.93	3.77	χ ² ₍₆₎ = 13.040*
Vk	Male	2.20	1.40–3.60	1.66	χ ² ₍₅₎ = 1.025
	Female	4.20	2.60–6.80	4.96	χ ² ₍₄₎ = 0.242

* Significant heterogeneity at *P* < 0.05.

TABLE 8
Comparison of Insecticidal Activity of the Synthesized Compounds with
Certain Standards against *Chrysomya albiceps* Larvae

Comp.	LD ₅₀ (μ g per larva)	95% fiducial limit (μ g per larva)	Slope	χ^2 (d.f.)
Malathion	136.14	80.22–230.92	1.11	$\chi^2_{(4)} = 1.728$
Propoxur	12.01	7.79–18.48	1.01	$\chi^2_{(4)} = 4.515$
Va	581.60	341.18–750.21	2.98	$\chi^2_{(6)} = 3.610$
Vc	654.50	421.51–891.41	1.83	$\chi^2_{(6)} = 9.060$
Vj	423.03	269.97–641.08	2.52	$\chi^2_{(6)} = 5.130$
Vk	230.00	131.13–373.46	3.48	$\chi^2_{(6)} = 4.120$

ity against the blow fly *Chrysomya albiceps* approximately equal to that of malathion. However all the four compounds are less potent than propoxur.

Table 8 shows that **Vk** is the most potent compound against the third-instar larvae although all the compounds were less effective than malathion or propoxur.

REFERENCES

1. Rao, R. P., Sharma, B. & Zaidi, N., Synthesis and anti-tubercular activity of some 2-alkylthio-3-aryl-4(3H)quinazolones. *Indian J. Chem.*, **16B** (1978) 1023–4.
2. El-Kerdawy, M. M., Abd-El-Kader, Ismail M. & Gineinah, M. M., A convenient synthesis of 3-aryl-1,2,4-triazolo[4,3-c]quinazolines. *J. Heterocyclic Chem.*, **27** (1990) 497–501.
3. Mahmoud, A. M., El-Sherief, H. A. H., El-Naggar, G. M. & Abd-El-Rahman, A. E., Synthesis of 5-mercapto-1,2,4-triazole derivatives containing 4(3H)-quinazolone nucleus. *Indian J. Chem.*, **22B** (1983) 491–3.
4. Badawy, M. A., Abdel-Hady, A. L. & Yehia, A. I., Chemistry of quinazolines; Reinvestigation of the action of hydrazine on thioxo derivatives. *J. Heterocyclic Chem.*, **22** (1985) 1535–6.
5. Misra, V. S., Saxena, V. K. & Srivastava, R., Synthesis of some *N'*-(2'-alkyl or aryl-6',8'-substituted quinazolone-3'-yl-aminoacetyl)-*N*³-aryl ureas and their *in-vivo* action on caecal amoebiasis of rats., *J. Indian Chem. Soc.*, **LX** (1983) 610–11.
6. Pawloski, C. E., Heterocyclic substituted triazolyl phosphorus compounds and their use as insecticides (Dow Chemical Co.) US 4, 298, 602 (Cl. 424-200; Co7D213/02) (1981); *CA*, **96** (1982) 85744a.
7. Sanemitsu, Y., Mizutani, M. & Nakayama, Y. A., Synthetic approach to novel S,N-heterocycles with biological activities. *Yuki Gosei Kagaku Kyokaiishi*, **50** (1992) 875–86 (Japanese); *CA*, **118** (1993) 6884t.
8. Gozzo, F., Boschi, P. M. & Longoni, A., 1,2,4-Triazole intermediate derivatives (Montedison S.P.A) Can. CA 1,106, 387 (Cl. Co7D249/12) (1981), IT Appl. 76/29,420 (1976); *CA*, **96** (1982) 122804t.
9. Parsons, J. H. & West, P. J., Pesticidal heterocyclic compounds, compositions containing them and their use (FBC Ltd.) Eur. Pat. Appl. EP 36, 711 (Cl. Co7D 249/08) (1981); G B Appl. 80,19769 (1980); *CA*, **96** (1982) 69002b.
10. Bhargava, P. N. & Srivastava, K. S. L., Synthesis of some new 6-iodo-2-thio-3-aryl-4-quinazolones. *Indian J. Chem.*, **6** (1968) 281–3.
11. Kottke, K., Kuhmstedt, H., Grafe, I., Knoke, D. & Schleuder, M., Über die Hydrazinolyse von 3-alkyl-und 3-Arylsubstituierten-4-Oxo-2-Thioxo-1,2,3,4-Tetrahydrochinazolinen. *Pharmazie*, **45** (1990) H.1.
12. Omar, A. H., Biological studies on the blow fly, *Chrysomya albiceps* (Wied.) in Egypt. M/Sc/Thesis, Fac. Sci., Cairo Univ., Egypt, 1974.
13. Finney, D. J., *Probit Analysis*. 3rd edn. Cambridge Univ. Press, New York, 1971.